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Lipid-Based Nanocarriers for Dual Modulation of Lipid Metabolism and Glucose Homeostasis

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ABSTRACT

Lipid metabolism and glucose homeostasis are two intertwined metabolic processes that are often dysregulated in conditions such as obesity, insulin resistance, and type 2 diabetes (T2D). Given the complexity of these disorders, therapeutic strategies targeting both lipid and glucose metabolism are critical for effective management. Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), offer promising platforms for the dual modulation of lipid metabolism and glucose homeostasis. These nanocarriers can encapsulate bioactive compounds that regulate lipid and glucose pathways, provide targeted delivery to specific tissues, and enhance the bioavailability and therapeutic effects of drugs. This review explores the role of lipid-based nanocarriers in the dual modulation of lipid metabolism and glucose homeostasis, highlighting their mechanisms of action, therapeutic applications, and the challenges associated with their development and clinical translation.

Keywords: lipid metabolism, glucose homeostasis, nanocarriers, liposomes, insulin resistance, type 2 diabetes

INTRODUCTION

The regulation of lipid metabolism and glucose homeostasis is fundamental to maintaining metabolic health[1–4]. Dysregulation of these processes is central to the pathophysiology of common metabolic disorders such as obesity, insulin resistance, and type 2 diabetes (T2D). In these conditions, insulin resistance leads to impaired glucose uptake by peripheral tissues (muscle, liver, and adipose tissue) and disrupted lipid metabolism, resulting in hyperglycemia, dyslipidemia, and chronic low-grade inflammation. These metabolic disturbances significantly increase the risk of cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and other complications[5-7].

The interplay between lipid metabolism and glucose homeostasis is crucial in the development of insulin resistance and obesity. Insulin resistance leads to a shift in lipid metabolism, characterized by increased fatty acid oxidation, lipogenesis, and the accumulation of intracellular lipids in tissues such as the liver and muscle[8, 9]. This results in lipotoxicity, which further impairs insulin signaling and worsens glucose control. Additionally, dysregulated adipose tissue function including the release of pro-inflammatory adipokines—exacerbates systemic inflammation and insulin resistance.

Current therapeutic strategies primarily focus on improving insulin sensitivity through lifestyle modifications, medications such as metformin, and insulin therapy. However, these treatments often fail to simultaneously address the underlying lipid metabolic disturbances that contribute to obesity and T2D[10, 11]. Lipid-based nanocarriers provide an innovative approach to targeting both lipid metabolism and glucose homeostasis, offering the potential for dual-modulation therapy[12-14].

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), are well-suited for this dual modulation due to their ability to encapsulate both hydrophilic and hydrophobic bioactive compounds. These carriers offer targeted drug delivery, enhanced bioavailability, and the ability to modify drug release kinetics, allowing for controlled and sustained therapeutic effects[12, 15]. Moreover, their biocompatibility, safety, and ability to target specific tissues (such as adipose, liver, and muscle) make lipid-based nanocarriers promising candidates for improving metabolic control in patients with insulin resistance and related disorders. This review explores the potential of lipid-based nanocarriers in modulating both lipid metabolism and glucose homeostasis. We will examine the mechanisms through which these nanocarriers function, the therapeutic agents they can deliver, and the challenges associated with their

development and clinical translation. We will also highlight the latest advancements in the use of lipid-based nanocarriers for the treatment of obesity, insulin resistance, and T2D.

2. Mechanisms of Action of Lipid-Based Nanocarriers

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), offer several advantages in targeting both lipid metabolism and glucose homeostasis[16–20]. These nanocarriers possess unique properties, such as biocompatibility, stability, high encapsulation efficiency, and the ability to release therapeutic agents in a controlled manner. The mechanisms by which lipid-based nanocarriers modulate lipid and glucose metabolism primarily involve targeted delivery, enhanced bioavailability, and the controlled release of bioactive compounds that regulate these pathways[20, 21].

Targeted Delivery to Metabolic Tissues

Lipid-based nanocarriers can be engineered to target specific metabolic tissues, such as adipose tissue, muscle, and liver, which are central to lipid and glucose metabolism. Targeting these tissues is critical for enhancing the efficacy of treatments for insulin resistance, obesity, and dyslipidemia[17, 22, 23]. Nanocarriers can be functionalized with specific ligands or surface modifications that facilitate selective binding to receptors overexpressed in these tissues. For example, PEGylation of nanoparticles enhances their circulation time, while targeting ligands such as fatty acid receptors or GLUT4 (glucose transporter) can direct nanocarriers to insulin-sensitive tissues.

Enhanced Bioavailability of Therapeutic Agents

Many therapeutic agents used to modulate lipid and glucose metabolism have poor solubility and bioavailability. Lipid-based nanocarriers can encapsulate hydrophobic drugs, such as statins, PPAR agonists, and antioxidants, improving their stability, solubility, and absorption. For example, liposomal formulations of omega-3 fatty acids or curcumin have shown enhanced bioavailability compared to their free forms, leading to more effective modulation of lipid metabolism and insulin sensitivity[24, 25]. These nanocarriers also provide a platform for co-delivering multiple bioactive compounds that target different aspects of metabolic dysfunction, allowing for a more comprehensive approach to therapy.

Controlled and Sustained Release of Therapeutic Agents

One of the key advantages of lipid-based nanocarriers is their ability to provide controlled and sustained release of encapsulated agents[26]. This feature is particularly important for therapies aimed at modulating lipid metabolism and glucose homeostasis, as prolonged exposure to therapeutic agents can enhance their effectiveness while minimizing side effects. For instance, SLNs and NLCs have been used to deliver PPAR agonists (such as pioglitazone) and fibrates to regulate lipid storage and improve insulin sensitivity[26]. These nanocarriers can provide a sustained release of the drug, ensuring prolonged action and reducing the frequency of administration.

Moreover, lipid-based nanocarriers can be engineered to release their payload in response to specific stimuli, such as changes in pH or temperature, which are characteristic of inflamed or insulin-resistant tissues[27, 28]. This stimulus-responsive release ensures that therapeutic agents are released at the site of action, maximizing their therapeutic effects while minimizing off-target effects.

3. Lipid-Based Nanocarriers for Modulation of Lipid Metabolism

Lipid metabolism plays a central role in the pathogenesis of obesity, insulin resistance, and type 2 diabetes (T2D). Dysregulated lipid metabolism contributes to the accumulation of intracellular lipids, which leads to lipotoxicity, mitochondrial dysfunction, and insulin resistance[29]. Lipid-based nanocarriers offer a promising strategy for targeting lipid metabolic pathways and restoring balance. These nanocarriers can deliver a wide range of bioactive compounds that modulate fatty acid oxidation, lipogenesis, and lipid storage[29].

Targeting Fatty Acid Oxidation

One of the key mechanisms through which lipid-based nanocarriers can modulate lipid metabolism is by enhancing fatty acid oxidation in insulin-sensitive tissues such as muscle and liver. PPAR agonists (such as fibrates) are widely used to regulate lipid metabolism by activating peroxisome proliferator-activated receptors (PPARs), which promote fatty acid oxidation and reduce triglyceride levels[30]. Lipid-based nanocarriers, such as liposomes or SLNs, can encapsulate PPAR agonists, allowing for targeted delivery to adipose tissue, muscle, and liver, thereby enhancing their effectiveness. These nanocarriers can also improve the bioavailability and stability of these agents, ensuring sustained activation of PPARs and improved metabolic outcomes[30].

Regulation of Lipogenesis

In obesity and T2D, lipogenesis (the process of converting excess glucose into fat) is often upregulated, leading to increased fat storage in adipose tissue and visceral fat accumulation [31, 32]. Lipid-based nanocarriers can deliver anti-lipogenic agents such as metformin or curcumin, which inhibit lipogenesis and promote fat mobilization[33]. For example, liposomal curcumin has been shown to reduce adiposity and hepatic steatosis by inhibiting lipogenic enzymes and promoting fat oxidation. By targeting the liver and adipose tissue, lipid-based nanocarriers can regulate fat storage and improve insulin sensitivity, ultimately leading to better control of glucose metabolism[33].

Prevention of Lipotoxicity

Lipotoxicity, caused by the accumulation of free fatty acids in non-adipose tissues such as the liver and muscle, contributes to insulin resistance and metabolic dysfunction[34]. Lipid-based nanocarriers can be used to deliver

antioxidants (such as alpha-lipoic acid or vitamin E) to neutralize reactive oxygen species (ROS) and reduce oxidative stress. By targeting the delivery of antioxidants to insulin-resistant tissues, lipid-based nanocarriers can help prevent lipotoxicity, improve mitochondrial function, and restore glucose homeostasis[34]. These nanocarriers can also protect against inflammatory cytokine release, which exacerbates insulin resistance and impairs lipid metabolism.

4. Lipid-Based Nanocarriers for Modulation of Glucose Homeostasis

Glucose homeostasis is tightly regulated by insulin, which facilitates glucose uptake into insulin-sensitive tissues such as muscle, liver, and adipose tissue. In obesity and type 2 diabetes (T2D), insulin resistance disrupts this process, leading to hyperglycemia and impaired glucose control[35, 36]. Lipid-based nanocarriers can modulate glucose homeostasis by targeting insulin signaling pathways, improving insulin sensitivity, and enhancing glucose uptake in insulin-resistant tissues.

Insulin Sensitization

Lipid-based nanocarriers can deliver insulin-sensitizing agents, such as thiazolidinediones (TZDs) or metformin, to improve insulin action in peripheral tissues. TZDs, which activate PPARγ, enhance insulin sensitivity by increasing glucose uptake and reducing hepatic glucose production[37]. By encapsulating these agents in lipid-based nanocarriers, such as liposomes or NLCs, it is possible to improve their bioavailability, reduce side effects, and enhance tissue-specific targeting, particularly to adipose tissue and the liver. The sustained release of insulin-sensitizing agents from these nanocarriers ensures prolonged therapeutic effects and better control of glucose levels[37, 38].

Targeted Glucose Uptake

Nanoparticles can also enhance glucose uptake in insulin-sensitive tissues by delivering glucose transporter activators. For example, berberine, a natural compound known to activate AMP-activated protein kinase (AMPK) and increase GLUT4 translocation, can be encapsulated in lipid-based nanocarriers for targeted delivery to muscle and adipose tissue[39, 40]. By promoting glucose uptake through enhanced GLUT4 activity, lipid-based nanocarriers can improve glucose metabolism and reduce hyperglycemia in insulin-resistant individuals.

Reduction of Hepatic Glucose Production

In obesity and T2D, the liver becomes resistant to insulin's inhibitory effect on glucose production (gluconeogenesis). Lipid-based nanocarriers can deliver AMPK activators or sirtuin activators (such as resveratrol), which promote glucose utilization and reduce hepatic glucose production. By delivering these agents directly to the liver, lipid-based nanocarriers can enhance insulin sensitivity in hepatic tissue, improve glucose control, and reduce the risk of hyperglycemia[12, 24, 26].

5. Challenges and Future Directions

While lipid-based nanocarriers offer significant potential in the dual modulation of lipid metabolism and glucose homeostasis, several challenges must be addressed before these therapies can be widely adopted in clinical practice.

Biocompatibility and Safety

The biocompatibility and safety of lipid-based nanocarriers are crucial for their clinical application. Nanoparticles must be designed to minimize immune responses, toxicity, and accumulation in non-target tissues. Long-term studies are necessary to assess the biodegradability and clearance of nanocarriers, as well as their potential to induce side effects in the liver, kidney, or other organs.

Targeting Specificity

One of the major challenges in developing effective lipid-based nanocarriers is ensuring their targeting specificity. Lipid nanocarriers must be able to selectively deliver their payload to insulin-sensitive tissues (adipose tissue, liver, muscle) without affecting other tissues. Advances in surface functionalization and the use of targeting ligands (such as antibodies or peptides) can improve the selectivity of lipid-based nanocarriers and enhance their therapeutic efficacy.

Scalability and Manufacturing

The scalable production of lipid-based nanocarriers that meet clinical standards is a significant challenge. The production process must ensure consistent quality, stability, and high encapsulation efficiency while maintaining the biocompatibility of the nanocarriers. Additionally, large-scale manufacturing must be cost-effective to make these therapies accessible to patients.

Clinical Translation

Despite promising preclinical results, the translation of lipid-based nanocarriers into clinical practice requires overcoming regulatory hurdles. The regulatory approval of lipid-based nanotherapies will depend on comprehensive clinical trials that demonstrate their efficacy, safety, and long-term effects in humans. Moreover, the cost-effectiveness of these therapies must be evaluated to ensure that they are viable for widespread use.

CONCLUSION

Lipid-based nanocarriers offer an innovative approach to the dual modulation of lipid metabolism and glucose homeostasis, addressing the root causes of obesity, insulin resistance, and type 2 diabetes (T2D). By delivering insulin-sensitizing agents, lipid-lowering drugs, and antioxidants, lipid-based nanocarriers have the potential to restore metabolic balance and improve glucose control in insulin-resistant individuals. The ability of these

nanocarriers to target specific metabolic tissues, enhance bioavailability, and provide controlled drug release makes them highly promising for the treatment of metabolic disorders. However, several challenges remain in developing lipid-based nanocarriers for clinical use, including issues related to biocompatibility, targeting specificity, scalability, and regulatory approval. Future research should focus on improving the efficiency of nanoparticle delivery systems, enhancing targeting precision, and conducting large-scale clinical trials to establish the safety and effectiveness of these therapies. In conclusion, lipid-based nanocarriers hold immense potential in revolutionizing the treatment of obesity and T2D by targeting the underlying metabolic dysfunctions. With continued advancements in nanotechnology, these therapies could provide personalized and effective treatments for improving insulin sensitivity, lipid metabolism, and glucose homeostasis.

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